Common carotid intima-media thickness relates to cardiovascular events in adults under the age of 45 years

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Abstract

Although atherosclerosis starts in early life, evidence on risk factors and atherosclerosis in individuals under 45 years of age is scarce. Therefore, we studied the relation between risk factors, common carotid intima-media thickness (CIMT) and first-time cardiovascular events in adults under 45 years of age.

Our study population consisted of 3067 adults under 45 years of age free from symptomatic cardiovascular disease at baseline, derived from 6 cohorts that are part of the USE-IMT initiative, an individual participant data meta-analysis of general-population based cohort studies evaluating CIMT measurements. Information on risk factors, CIMT measurements and follow-up of the combined endpoint (first-time myocardial infarction (MI) or stroke) was obtained. We assessed the relation between risk factors and CIMT and the relation between CIMT and first-time MI or stroke using a multivariable linear mixed-effects model and a Cox proportional-hazards model respectively.

During a follow-up of 16.3 years, 55 first-time MIs or strokes occurred. Median CIMT was 0.63 mm. Of the risk factors under study, age, sex, diastolic blood pressure, body mass index, total cholesterol and high-density lipoprotein cholesterol related to CIMT. Furthermore, CIMT related to first-time MI or stroke with a hazard ratio of 1.40 per standard deviation increase in CIMT, independent of risk factors ([95% confidence interval: 1.11, 1.76]).

CIMT may be a valuable marker for cardiovascular risk in adults under 45 years of age who are not yet eligible for standard cardiovascular risk screening. This is especially relevant in those with an increased, unfavorable risk factor burden.

Key words: intima media thickness, events, risk factors, atherosclerosis, young adults

Introduction

Despite evolution in management of known cardiovascular (CV) risk factors, cardiovascular disease (CVD) remains the leading cause of morbidity and mortality worldwide.[1] Atherosclerosis, the pathophysiology underlying the majority of CV events, is a progressive inflammatory condition that causes detrimental remodeling of various vascular walls. Atherosclerosis begins early in life, yet develops over decades as a clinically silent disease, providing the opportunity for preclinical identification of high-risk individuals and early initiation of preventive strategies.[2]

Currently, preclinical identification of high-risk individuals is based on risk assessment using scoring systems of aggregated CV risk factors.[3, 4] Nevertheless, risk factor profiling alone cannot conclusively identify individuals at highest risk for developing clinically manifest CVD.[5] Furthermore, these scoring systems are mostly used in individuals over 40 years of age. Moreover, associations between risk factors and clinically manifest CVD have primarily been established in people over 45 years of age. Data from long-term observational studies on CV risk assessment in younger adults are limited.[6]

Finding proxies that reliably detect subclinical atherosclerosis early in life is important since preventive regimens started early in life might delay the development of clinically manifest CVD. The American Heart Association (AHA) acknowledges this and emphasizes on increased evaluation of noninvasive methods for CV risk assessment in the young to achieve increased preclinical identification of high-risk individuals years before clinically manifest CVD arises.[7]

Carotid intima-media thickness (CIMT), measured non-invasively using B-mode ultrasonography, is an established marker for subclinical atherosclerosis. Research demonstrates that already from a young age onwards, CIMT relates to various CV risk factors.[8-10] However, whereas the relation between increased CIMT and events has consistently been demonstrated for middle age and elderly subjects, information to support a relation between CIMT and actual CV events in younger adults is absent.[11] Showing this relation is the first step in the process of finding proxies that reliably detect subclinical atherosclerosis early in life.

Therefore, this study evaluates the relation between CV risk factors, CIMT and CV events in adults under 45 years of age.

Methods

Study design and study population

Our study population comprised adults under 45 years of age, free from symptomatic CVD at baseline who are participating in general-population based cohort studies that share their data in the USE-IMT initiative. The ongoing USE-IMT research collaboration, initiated in 2007**,** is a global meta-analysis project using individual participant data from several prospective population based cohort studies to determine the added value of CIMT to current risk prediction models in asymptomatic individuals at risk for CVD. Study rationale and description are published elsewhere.[12-14] In short, cohorts eligible for participation in USE-IMT were identified through literature searches of database and expert suggestion and required to comprise participants who were drawn from the general population, have baseline data available on CV risk factors such as age, sex, cigarette smoking, antihypertensive medication use, blood pressure, cholesterol fractions, CIMT measurements, history of CVD and diabetes mellitus and follow-up information on occurrence of fatal and non-fatal CV events and death. Individual data from cohorts were obtained and integrated for statistical analyses using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). USE-IMT currently comprises 17 participating cohorts with in total ~74.000 individuals.

For our study, individuals were eligible for participation if they were aged between 18 and 45 years and free from symptomatic CVD at baseline. These inclusion criteria were met by participants from 6 cohorts: the Carotid Atherosclerosis Progression Study (CAPS), the Firefighters and Their Endothelium Study (FATE), the Kuopio Ischemic Heart Disease Risk Factor Study (KIHD), the Osaka Follow-up Study for

Carotid Atherosclerosis 2 (OSACA2 Study), the Tromsø Study and the Charlottesville Study, comprising in total 3106 individuals in our study. Study design and detailed description for each of these cohorts is described elsewhere and in the online-only supplement.[14-20] Incomplete data on mean common CIMT, risk factors and (time to) event were imputed per cohort (single imputation in the multivariate imputation by chained equations [MICE] package of R statistical software, version 2.10.0, Vienna, Austria) as described previously.[21] In 39 subjects, the required information for our analyses was missing. Therefore, complete case multivariable analysis was performed in 3067 subjects.

Risk factor measurements

The required information on baseline demographic characteristics namely age, sex, cigarette smoking, history of hypertension, antihypertensive and lipid lowering medication use and diabetes status was present in all participating cohorts. The definition of diabetes mellitus differed between cohorts and is shown elsewhere.[13] Furthermore, data on the following measurements were available in all cohorts: height, body weight, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP) and serum lipid levels. Moreover, mean common CIMT was measured. Detailed information on CIMT methodology used in each cohort has been published previously.[13] In short, baseline CIMT was measured non-invasively using ultrasound imaging. Average mean common CIMT was calculated per individual using the maximum set of carotid angles, near and/or far wall measurements and left and/or right side measurements that were assessed within each cohort. This method is based on the observation that the magnitude of the relation between common CIMT and the risk of CV events does not differ much across different measures.[22]

Atherosclerotic plaques and CIMT assessments from different sites than the common carotid segment were not considered in this analysis, since data were not available for all cohorts.

CV endpoint

Time to first event was defined as time to first-time myocardial infarction (MI) or stroke, included as a combined endpoint, comprising both fatal and non-fatal events. When a participant experienced multiple events, time-to-event was defined as time to the first of these events. The endpoint was constructed using each cohort's original event definitions and variables, presented in the online-only supplement.[15-20] Definitions for MI were based on International Statistical Classification of Diseases and Related Health Problems (ICD-9 and ICD-10) codes, autopsy reports or a combination of changes in cardiac biomarker levels with clinical symptoms and signs and/or pathological ECG findings and/or positive imaging tests. Definitions of stroke were based on ICD-9 and ICD-10 codes, autopsy reports or a combination of clinical symptoms and abnormalities on neurovascular imaging. We included only MI and stroke since these endpoints are major events, were available in all cohorts and are least likely to be affected by differences in adjudication of endpoints across cohorts.

Follow-up and censoring

In each cohort, CIMT was measured at baseline. Individuals were censored when they suffered from a non-fatal or fatal CV event, died due to any cause, reached the end of the study period or were lost to follow-up due other reasons (e.g. moving out of the district). For each individual, follow-up time was estimated based on baseline data and censoring data (online-only supplement).

This study was approved by an institutional review committee (online-only supplement). Each individual cohort obtained approval from a local Ethical Review Board and written informed consent from all participants. All authors exchanged a material transfer agreement.

Data analysis

Baseline demographic characteristics of the studied participants, including risk factors, were summarized using medians with interquartile ranges or percentages. To evaluate which CV risk factors related to CIMT, we adjusted for differences in baseline measurement of common CIMT between studies. Subsequently, we adjusted common CIMT for age and sex within studies. Therefore, we split our data into age-categories (18-24, 25-29, 30-34, 35-39, 40-45 years), sex and study and created an age-category, sex and study-specific mean common CIMT, the ´adjusted common CIMT`. Subsequently, within each subset, we identified individuals with an 'adjusted common CIMT' below and individuals with an 'adjusted common CIMT' above the 50th percentile. Because CIMT was non-normally distributed, we used Mann-Whitney U tests for continuous variables and X^2 tests for categorical variables to assess differences in risk factor levels between these two groups. Risk factors that were significantly unequally distributed between individuals with an 'adjusted common CIMT' below and individuals with an 'adjusted common CIMT' above the 50th percentile, applying a selection criterion of $p<0.2$ for inclusion, were potential determinants of CIMT and included in the linear mixed-effects model together with the variables age, sex and study. The unequally distributed risk factors were BMI, SBP, DBP, total cholesterol and high-density lipoprotein (HDL) cholesterol levels, history of hypertension, presence of diabetes and antihypertensive medication use

(online-only supplement). Due to the expected multicollinearity between SBP and DBP, we included only DBP in our multivariable models. Although smoking and lipid lowering medication use did not relate to common CIMT, but are clearly determinants of outcome, we included these variables as well.

The relation between the selected CV risk factors and mean common CIMT was studied using a multivariable linear mixed-effects model with a random intercept for study to correct for heterogeneity in mean common CIMT across cohorts. To meet the mandatory criteria for linear mixed-effects models, natural logarithmic transformation of the variable mean common CIMT was used.

The relation between mean common CIMT and time to first event was analyzed using an age and sex adjusted and a multivariable (adjusted for the selected risk factors) Cox proportional-hazards model that included cohort as a random effect using the frailty model. Heterogeneity in mean common CIMT and events across cohorts was tested with a likelihood ratio test for interaction between cohort and mean common CIMT. Conclusions were based on p values and standardized β regression coefficients (beta's) and standardized hazard ratio's (HR) respectively, both with 95% confidence intervals. We checked the proportional-hazards assumption in the adjusted models using Lowess curves and found no violations. Statistical significance was defined as $p^{2\ sided}<0.05$. Data analyses were conducted using the statistical environment R (version 2.3.1).

Results

Demographic characteristics of the participants are displayed in Table 1. Of 3067 eligible participants, 1239 (40%) were women. Median age was 37 years (32, 42). Average mean common CIMT was 0.63 mm (0.56, 0.68). Median follow up time was 8.6 years during which 55 out of 3067 (1.8%) participants had a first-time MI or stroke. The total number of person-years was 27579, the incident rate of first-time MI or stroke per 10.000 person-years was 20.

The multivariable linear mixed-effects model demonstrated a relation between log transformed mean common CIMT and age (β = 0.041 mm increase in log-CIMT per 1 standard deviation (SD) increase in age, [0.036, 0.047]), sex (β = 0.013 mm increase in log-CIMT in males as compared to females, [0.001, 0.025]), DBP (β = 0.008 mm increase in log-CIMT per SD increase in DBP, [0.003, 0.014]), BMI (β = 0.014 mm increase in log-CIMT per SD increase in BMI, [0.009, 0.020]), total cholesterol (β = 0.009 mm increase in log-CIMT per SD increase in total cholesterol level, [0.004, 0.014]) and HDL-cholesterol level (β = 0.068 mm decrease in log-CIMT per SD increase in HDL-cholesterol level, [-0.013, -0.001]) (Table 2).

The multivariable Cox proportional-hazards model showed that mean common CIMT significantly related to incident MI or stroke with a HR of 1.40 per 1 SD increase in CIMT [1.11, 1.76] (Table 3). Furthermore, each quartile increase in CIMT (using the first quartile (Q1) as the reference category) increased the hazard on incident MI or stroke with HRs of 1.49 [0.49, 4.53], 2.22 [0.78, 6.29] and 3.04 [1.11, 8.32] respectively (online-only supplement).

Of note, there was no evidence for heterogeneity in the relation between mean common CIMT and outcome between studies since the likelihood ratio test for interaction was not significant (p=0.69), neither was the frailty of the model (p = 0.19).

Discussion

Data from long-term observational studies on CV risk assessment in younger adults are limited.[5, 6] This study based on 3067 participants from 6 cohorts demonstrates that an increased mean common CIMT positively relates to first-time MI or stroke in adults under 45 years of age and free of symptomatic CVD, independent from established cardiovascular risk factors. Furthermore, of the CV risk factors under study, age, sex, DBP, BMI, total cholesterol and HDL-cholesterol levels related to mean common CIMT.

Atherosclerosis directly affects various arterial walls. Arterial wall thickness is assumed to represent atherosclerosis and therefore (subclinical) CVD risk. CIMT independently relates to vascular risk factors, atherosclerotic plaques and incident stroke and MI.[8-10] Furthermore, evidence of atherosclerosis in the carotid artery reflects atherosclerosis elsewhere in the vasculature, mainly in the coronary arteries and the aorta. Evidence from studies in older individuals indeed showed a clear relation between increased CIMT and atherosclerosis in the coronary and peripheral arteries.[22, 23] Therefore, CIMT is increasingly used as a surrogate marker of CVD risk and as an outcome measure in clinical trials (i.e. measuring changes in CIMT in response to medication or interventions).[11, 24]

Associations between risk factors and clinically manifest CVD have extensively been studied in older adults.[6] These studies demonstrated that an adverse CV risk burden associates with presence and extent of atherosclerosis.[11, 13, 14] Studies performed in younger adults documented a strong relation between CIMT and the CV risk factors age, sex, BMI, SBP, total cholesterol, LDL-cholesterol, HDL-cholesterol, smoking and

presence of diabetes.[8-10] Our study agrees with these data to a large extent. The lack of a relation between smoking and mean common CIMT might be due to an insufficient number of years of smoking exposure and to a lack of information on pack years in our study population. Furthermore, the low number of participants with diabetes in our study (*n=22*) is a possible explanation for the absence of a significant relation between the presence of diabetes and mean common CIMT. Moreover, SBP is generally accepted as a more important risk factor than DBP. However, we adjusted our multivariable models for DBP since previous research demonstrated that DBP may be a more important marker than SBP in CV risk assessment in subjects under 45 years of age.[25] Although modeling DBP instead of SBP attenuated our associations, it did not affect our results significantly (online-only supplement). Both measurements significantly relate to CIMT and not significantly to incident MI or stroke.

To our knowledge, we are among the first to report on the relation between CIMT and incident CV events in adults under 45 years of age. This lack of scientific evidence seems logical given that CV endpoints are scarce in young individuals and cohort studies would require extremely long follow-up time and/or many individuals involved. The latter can be easily achieved by pooling of individual participant data. As mentioned afore, in older adults, CIMT has consistently been related to clinical outcomes such as MI and stroke.[11, 13, 14] We extend these results to younger populations, supporting the view that CIMT is a particularly interesting outcome in research performed in the young. We demonstrated that mean common CIMT relates to CV events in individuals under 45 years of age. One SD increase in mean common CIMT leads to a 40% increase in the risk of developing a stroke or MI,

independent of established CV risk factors. Moreover, except for antihypertensive or lipid lowering medication use, individual risk factors did not relate to first-time MI or stroke. However, risk factors aggregated in a CIMT measurement did relate to first-time MI or stroke, implying that the expansion of the CV risk factor load within a young individual works synergistically on the risk for developing CVD. Furthermore, whereas risk factors are merely cross sectional measurements, a CIMT measurement incorporates a time effect since CIMT increases with an increased time of exposure to (an increased load of) risk factors. Hence, in younger adults, CIMT may be a valuable marker for CVD risk, especially in those who have an increased risk factor burden. Unfortunately, due to the low number of events (*n=55*), we were unable to adequately assess the added value of CIMT measurements in CV risk assessment through evaluating calibration, discrimination or reclassification improvement. A study with more events and likely a larger sample size is needed.

This study has several strengths. The USE-IMT initiative consists of multiple collaborating cohorts.[13, 14] Furthermore, we used the mean common carotid artery for our CIMT measurements. These measurements were obtained in all cohorts and are feasible to apply in clinical practice since the common carotid artery is more easily accessible than the bifurcation or internal carotid artery and has a high reliability of measurement.[26]

Our study has limitations. The protocols used to evaluate mean common CIMT differed between studies, which may have caused higher variance of the CIMT assessment and thus an underestimation of the relations found in this study. In addition, due to lack of data, we were unable to include other cardiovascular risk

factors, such as waist circumference, alcohol intake and sedentariety in our analysis. Moreover, we restricted our CIMT measurements to the mean common carotid artery since this was the only measurement obtained in all 6 cohorts. Therefore, we are unable to determine the value of an ultrasonographically acquired CIMT measured at locations other than the mean common carotid artery. This remains to be assessed. Furthermore, in the participating USE-IMT cohorts, information on other relevant CV endpoints was not available (e.g. heart failure, sudden cardiac death, peripheral arterial disease). However, given the low incidence of disease, it is unlikely that the lack of information on these outcomes has affected our estimates. If anything, an underestimation may have resulted. Finally, due to the low number of events, we are unable to provide information regarding the incremental value of CIMT beyond conventional risk factors and thus cannot provide recommendations for clinical applicability. However, showing a relation between CIMT and actual events in this young population is the first step in the process of finding proxies that reliably detect subclinical atherosclerosis early in life.

In conclusion, CIMT may be a valuable marker for CVD risk in adults under 45 years of age who are not yet eligible for standard cardiovascular risk screening, especially in those who have an increased risk factor load.

Perspectives

Our study suggests that a CIMT measurement may be a valuable marker for CVD risk in younger adults, specifically in individuals with an increased risk factor load. Although our study is too small to provide information regarding the incremental value of CIMT beyond conventional risk factors and thus cannot provide recommendations for clinical applicability, it is the first to show in this relatively young population that CIMT relates to CV events. Since the disease pattern of atherosclerosis provides the opportunity for preclinical identification and early initiation of preventive strategies in high-risk individuals, which may be most effective when initiated at a young age, showing such a relation is the first step in the process of finding proxies that reliably identify individuals at high-risk for developing clinically manifest CVD early in life.

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Novelty and Significance

What is New?

- Carotid-intima media thickness relates to cardiovascular events in adults under 45 years of age
- Expanded cardiovascular risk factor load within a young individual increases the risk for developing an event

What is Relevant?

- Data on noninvasive methods for evaluation of cardiovascular risk in younger adults are limited
- Standard risk profiling is rarely performed in younger adults and inconclusive
- Increased identification of younger adults at high-risk for cardiovascular disease may lead to early prevention

Summary

- CIMT may be a valuable marker for cardiovascular risk in younger adults who are not yet eligible for standard risk profiling
- Especially in individuals with an increased risk factor burden